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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
|-----------------|-------------|----------------------|---------------------|------------------|

09/663,968

09/19/2000

Ping Yip

24736-2049

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EXAMINER

SKOWRONEK, KARLHEINZ R

ART UNIT

PAPER NUMBER

1631

MAIL DATE

DELIVERY MODE

12/15/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |   |                                  |  |
|------------------------------|---|----------------------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>09/663,968      | <b>Applicant(s)</b><br>YIP, PING |  |
|                              | <b>Examiner</b><br>KARLHEINZ R. SKOWRONEK | <b>Art Unit</b><br>1631          |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11 October 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 46-91 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 70 and 79 is/are allowed.
- 6) ☒ Claim(s) 46-63, 66-69, 72-78, 80, 81 and 84-91 is/are rejected.
- 7) ☒ Claim(s) 64, 65, 71, 82 and 83 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>03/22/08</u> .  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Claim Status***

Claims 46-91 are pending.

Claims 1-45 are cancelled.

Claims 46-91 have been examined.

Claims 46-63, 66-69, 72-78, 80, 81, and 84-91 are rejected.

Claims 64, 65, 71, 82, and 83 are objected to.

Claims 70 and 79 are allowed.

### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on 22 March 2008 was filed after the mailing date of the first action after RCE on 21 September 2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 74 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 74 recites the limitation "the signal to noise ratio" in line 16-17.

There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The following rejection has been modified from the previous Office Action.

Claims 46, 66-69, 72, 73, 77, 78, and 84-91 rejected under 35 U.S.C.

103(a) as being unpatentable over Green et al. (US PAT 5, 853,979), in view of Dunkel (US PAT 5,572,125).

The claims are directed to an automated method, computerized system, system, and machine-readable program operating on a computer for identifying a component in a DNA sample using a mass spectrometer to generate a machine readable data set and analyzing the data by generating denoised data by performing noise reduction, correcting a baseline for the denoised data to generate an intermediate data set, defining peaks in the intermediate data set, subtracting the peaks from the intermediate data set to generate a residual data set, removing the residual data set from the intermediate data set to produce a corrected data set, locating peaks in the corrected data set and identifying the component that corresponds to each located peak.

Art Unit: 1631

Green et al. teach a method, a computerized system, system, and machine-readable program operating on a computer for identifying a component in a DNA sample using a mass spectrometer (col. 5, line 18 to generate a machine readable data set and analyzing the data by performing noise reduction to generate denoised data, correcting a baseline for the denoised experimental data representing an intermediate data set, defining peaks in the intermediate data set as "fragment pattern" (col. 5, lines 9-43). Green et al shows spectra can be "normalized" with fourth order polynomials (col. 11, line 36). Green et al. further teach the computer is integral to the instrument (cl. 85) (col. 16, line 27-39).

Green et al. do not teach the removal of peaks and subsequent generation and removal of a residual baseline from the denoised experimental data.

Dunkel et al. teach method of automated analysis and correction of spectral data obtained through ion cyclotron mass spectrometry (col. 1, lines 16-19). Dunkel shows that a mathematical model that describes the expected experimental spectral data is determined (col. 7, line 37-39). Dunkel shows that the best-fit mathematical model to the experimental data is subtracted from the experimental data to generate a residual (col. 9, line 10-13). Dunkel et al. teach that the residual baseline obtained by removing peaks from experimental data can be applied to the experimental data to correct for baseline distortion (col. 11, lines 2-3). Dunkel teach the generation of a residual baseline by subtracting modeled peak data from the experimental "intermediate" data (cls. 67-69) (col. 20, lines 40-45). Dunkel et al. teaches identifying includes identifying peak

Art Unit: 1631

probabilities for the putative peak and is derived using signal to noise ratio (cls. 77, 78, 88, 89, 90)(col.32, lines 27-29 and 48-51; and col. 33, lines 3 and 15-20). Dunkel shows baselines can be modeled as polynomial functions (col. 22, line58-61) Dunkel et al. teach the modeling of peaks by fitting a Gaussian curve (cl. 73) (col. 8, lines 5-7). Dunkel et al. teach performing a mass shift of the peak position (cl. 66) (col. 2, lines 43-46).

It would have been obvious to one of skill in the art to combine the method for correction of spectral data of Dunkel with the method intermediate data set generation of Green et al. because Green et al. teach that other signal processing techniques can be applied to generate clean, corrected data (col. 5, lines 47-49) and Dunkel teaches that baseline correction can be corrected by subtracting the residual baseline.

One would have been motivated to do so because Dunkel teaches that the residual baseline subtraction speeds up data analysis, improves the reliability of signal detection, and allows for the analysis of data sets of increased complexity (col. 33, lines 62-67).

### ***Response to Arguments***

Applicant's arguments filed 11 October 2007 have been fully considered but they are not persuasive. Applicant argues that Dunkel does not show the formation of a residual baseline by subtracting peaks from the experimental data or correction of the experimental data by subtracting the residual baseline. The argument is not persuasive. Dunkel shows that a mathematical model that describes the expected experimental spectral data is determined (col. 7, line 37-

Art Unit: 1631

39). Dunkel shows that the best-fit mathematical model to the experimental data is subtracted from the experimental data to generate a residual (col. 9, line 10-13). Dunkel is directed to the correction of spectral data. Spectral data can be, as demonstrated by Dunkel, described mathematically as complex wave forms. It is well known in the art that wave forms can be modeled with the components of amplitude, frequency, and phase, the most well known wave form being the Sine function,  $f(x) = A \cdot \sin(\omega \cdot x + \theta)$ , where A is the amplitude,  $\omega$  is the frequency and  $\theta$  is the phase. In figure 2, Dunkel shows wave forms that are common to spectroscopy. In a Cartesian coordinate system, the phase component of the wave form shifts the peaks along the abscissa or x-axis, the amplitude modifies the peak heights along the ordinate of y-axis, frequency modifies the distance between peaks. Applicant argues that mass spectrometer spectra have no phase information. The argument is not persuasive. The specification guides that due to calibration errors, the signal may be shifted left or right from the signals actual position and the putative peaks shifted such that they align more closely with the expected peaks (specification, p. 18, 10-14). What the specification is describing is equivalent to mathematically adjusting the phase of the model to more accurately model the experimental peaks.

The following rejection is reiterated from the previous Office Action.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US PAT 5, 853,979), in view of Dunkel (US PAT 5,572,125) as

Art Unit: 1631

applied to claim 46 above, and further in view of Stanton et al. (US PAT 6,440,705).

Claim 47 is directed to mass spectrometry that is MALDI-TOF.

Stanton et al. teach DNA analysis by MALDI-TOF mass spectrometry (col.9, lines 15-31).

It would have been obvious to one of skill in the art to combine the application of MALDI-TOF analysis of DNA of Stanton et al. with the method of mass spectrometry DNA spectral analysis of Green and the residual baseline generation of Dunkel et al. because Stanton et al. teach that MALDI-TOF is capable of ionizing DNA without further fragmentation (col. 9, line 22-23) whereas other mass spectrometry techniques can lead to further fragmentation (col. 16, line 60-62).

One would have been motivated with a reasonable expectation of success to do so because Stanton et al. teach the fulfillment of the need for a simple low cost, rapid, yet sensitive and accurate method for analyzing polynucleotides (col. 13, lines 43-46).

### ***Response to Arguments***

Applicant's arguments filed 11 October 2007 have been fully considered but they are not persuasive. Applicant argues that Stanton does not cure the deficiencies of Green in view of Dunkel. The argument is not persuasive because, as shown above, Green in view of Dunkel is not deficient in teaching.

The following rejection is reiterated from the previous Office Action.



Claims 48-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US PAT 5, 853,979), in view of Dunkel (US PAT 5,572,125) as applied to claim 46 above, and further in view of Shew et al. (US PAT 5,436,447).

The combination of references of Dunkel and Green et al. do not teach noise reduction (“denoising”) using wavelet technology transforms.

Shew et al. teach utilizing wavelet technology transforms to reduce noise in mass spectrometry data. Shew et al. teach the denoising includes the generation of a noise profile using wavelet technology in a series of stages or “transients” (cl. 48 and 49) (col. 7, lines 64-65). Shew et al. teach generating a noise profile for stage 0 i.e. the mother wavelet (cl. 50) (col. 3, lines 30-48). Shew et al. also teach generating other noise profiles by applying a scale factor to the stage 0 noise profile (cl. 51 and 52)(col. 8, line 61 and col. 3, lines 30-48). Shew et al. teach applying a threshold (“desired level”) to selected stages and added to the noise profile where the threshold is scaled before being applied and the scaling factors are less at higher stages (cl. 53-56) (col. 8, lines 55-60, col. 11, lines 5-7 and col. 16, lines 1-3). Shew et al. teach the generation of sparse data set (cl. 57) (col. 6, lines 19-26). Shew et al. teach shifting the denoised data (cl. 58) (col. 16, lines 41-45).

It would have been obvious to combine the wavelet technology to reduce noise in spectral data of Shew et al. with the method of mass spectrometry DNA spectral analysis of Green and the residual baseline generation of Dunkel et al. because Shew et al. teach wavelet technology transforms allow for more

Art Unit: 1631

accurate determinations for the relative ion abundances in a mass spectrometry sample (abstract).

One would have had a reasonable expectation of success and been motivated to do so by Dunkel who teaches that the method allows speeding up data analysis, improves the reliability of signal detection, and allows for the analysis of data sets of increased complexity (col. 33, lines 62-67). One would have also been motivated by Green et al. who teach increasing the speed of DNA sample analysis with improved accuracy (col. 3, line 17-20).

### ***Response to Arguments***

Applicant's arguments filed 11 October 2007 have been fully considered but they are not persuasive. Applicant argues that Shew does not cure the deficiencies of Green in view of Dunkel. The argument is not persuasive because, as shown above, Green in view of Dunkel is not deficient in teaching.

The following rejection is reiterated from the previous Office Action.

Claim 59-62 rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US PAT 5, 853,979), in view of Dunkel (US PAT 5,572,125) as applied to claim 46 above, and further in view of Gavin et al. (US PAT 6, 586, 728).

The combination of references of Dunkel and Green et al. do not teach the generating a moving average of the denoised data as a further correction of the baseline and identification of peaks. Green et al, however teaches that other signal processing techniques can be applied to generate clean, corrected data.

Art Unit: 1631

Gavin teaches the filtering of spectrometry data by application of a moving average filter to identify peak sections (col. 4, lines 8-25). Gavin et al. further demonstrate the application a moving average filter results in the smoothing of the spectral data and reduction of noise (figures 3-6).

It would have been obvious to combine the application of the moving average filter such as those described in Gavin et al. to improve the quality of the intermediate data set generation of Green et al. because Green et al. teach that other signal processing techniques can be applied to generate clean, corrected data (col. 5, lines 47-49), and by Gavin et al. who teach that the moving average filter optimizes the trade offs of increasing the signal to noise ratio and has the least negative effect on mass resolution (col. 3, line 19-24).

### ***Response to Arguments***

Applicant's arguments filed 11 October 2007 have been fully considered but they are not persuasive. Applicant argues that Gavin does not cure the deficiencies of Green in view of Dunkel. The argument is not persuasive because, as shown above, Green in view of Dunkel is not deficient in teaching.

The following rejection is newly applied.

Claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US PAT 5, 853,979), in view of Dunkel (US PAT 5,572,125) as applied to claim 46 above, and further in view of Ferrige et al. (Rapid Communication in Mass Spectrometry, Vol. 5, p. 374-377, 1991).

Claim 63 is directed to a method of identifying a component in a DNA sample comprising steps as in claim 46 and additionally requiring a step of compressing the intermediate data set.

Green et al. in view of Dunkel shows a method of identifying a component in a sample as applied to claim 46.

Green et al. in view of Dunkel does not show a step of data compression.

Ferrige et al. shows a mass spectrum deconvolution method called the maximum entropy (MaxEnt) technique. Ferrige et al. shows the MaxEnt technique compresses the intermediate data (p. 376, col. 2). Ferrige et al. shows that the MaxEnt technique is able to deconvolve noisy data much more effectively (p.374, col. 2). Ferrige et al. shows that the MaxEnt technique successfully enabled severely resolved peaks to be totally resolved (p. 377, col. 2).

It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method of identifying a component in a sample using a mass spectrometer of Green et al. in view of Dunkel with the MaxEnt deconvolution technique that compresses data of Ferrige et al. because Ferrige et al. shows that the MaxEnt technique is able to deconvolve noisy data much more effectively which successfully enabled severely resolved peaks to be totally resolved.

The following rejection is newly applied.

Claims 74-76 and 80-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US PAT 5, 853,979), in view of Dunkel (US PAT 5,572,125) as applied to claim 46 above, and further in view of Ferrige et al. (Rapid Communication in Mass Spectrometry, Vol. 6, p. 765-770, 1992) and in view of Gull et al. (IEEE Proc., Vol. 131, Pt. F, No. 6, p. 646-659, October 1984).

Claim 74 is directed to a method of identifying a component in a DNA sample comprising steps as in claim 46 and additionally requiring the identifying step use a generated noise profile to calculate a signal to noise ratio for the putative peak. In some embodiments, a peak error is calculated based on a comparison of the peak to a Gaussian curve. In an embodiment, the peak error is used to adjust the signal to noise ratio.

Claim 80 is directed to a method of identifying a component in a DNA sample comprising steps as in claim 46 and additionally requires the calculation of peak probability that a putative peak is a peak indicative of a component of the sample. In an embodiment, peak probability is calculated for a plurality peaks.

Green et al. in view of Dunkel shows a method of identifying a component in a sample as applied to claim 46.

Dunkel suggests that noise profiles can be simulated or “generated” and the simulated noise profiles used to create signal to noise ratios, “S/N ratio” (col. 32, line 40-45).

Green in view of Dunkel do not show a signal to noise ratio for a putative peak.

Ferrige et al. shows that the maximum entropy deconvolution technique uses a signal to noise ratio of a putative peak in a process of identifying peaks in mass spectrum data (p. 766, col. 1). Ferrige et al. shows that a generated noise profile in the form of an average noise level that is used to determine the signal to noise ratio for any particular peak (p. 766, col. 1). Ferrige et al. shows putative peaks are modeled as a Gaussian curve (p. 767, col. 1). Ferrige et al. suggests a peak error can be calculated from the fitted peak (p. 769, col. 2). Ferrige et al. suggests that signal to noise ratio is adjusted based on the peak error (p. 768, col. 2). Ferrige et al. shows the application of MaxEnt algorithm to high resolution mass spectrometry data is predictable, and any unknown or poorly known parameters relating to the instrument resolution/line shape function can be tuned objectively to the optimum values (p. 770, col. 1-2). With respect to claim 80, Ferrige et al. shows MaxEnt results in full probabilistic estimate of reliability (p. 770, col. 2). Ferrige et al. shows that the algorithm is guided to result in the most probable spectrum, reading on a peak probability indicative of sample composition (p. 769, col. 2).

Gull et al. shows maximum entropy provides a likelihood that the fitted data agrees with the experimental data (p. 646, col. 1-2). Gull shows maximum entropy is powerful method for reconstructing images from noisy and incomplete data (p. 646, col. 1 and abstract).

It would have been obvious to one of ordinary skill in the art to modify the method of identifying a component in a sample of Green et al. in view of Dunkel with the MaxEnt deconvolution technique of Ferrige et al. because Ferrige et al.

Art Unit: 1631

shows the application of MaxEnt algorithm to high resolution mass spectrometry data is predictable, and any unknown or poorly known parameters relating to the instrument resolution/line shape function can be tuned objectively to the optimum values.

### ***Allowable Subject Matter***

Claim 70 is allowed. The art does not fairly teach the removal of an area equal to twice the width of the Gaussian from the left of the center line of the putative peak.

Claim 79 is allowed. The art teaches the determination of allelic ratios on the basis of peak height (see for example Zauber et al., Molecular Diagnosis, Vol. 4, No. 1, p. 29-35, 1999) and determination of peak probabilities as in Ferrige et al.). The art does not show that peak probabilities can be calculated from allelic ratios.

Claims 64, 65, 71, 82, and 83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571) 272-9047. The examiner can normally be reached on 8:00am-5:00pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The

Art Unit: 1631

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KARLHEINZ R SKOWRONEK/  
Examiner, Art Unit 1631

15 December 2008